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Evaluating the effectiveness of conjugated pneumococcal vaccines in Colombia

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Abstract
A retrospective cohort study was conducted in 2631 Colombian children <2 yrs to evaluate pneumococcal vaccine effectiveness. Association between vaccination and disease was evaluated using Cox proportional hazards models. Vaccinated children had a significant reduction in hospitalization risk for all outcomes (HR 0,59 CI 95% 0,42 - 0,85) and for pneumonia the reduction was slightly higher (HR 0 ,53 CI 95% 0,32 - 0,89). Our results show an important risk reduction in clinical syndromes potentially associated to pneumococcus in vaccinated children confirming the benefits of using conjugate vaccines in a medium income developing country.

Keywords: Streptococcus pneumoniae; Pneumococcal Infections; Pneumococcal Vaccines; Vaccine effectiveness.

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1. Introduction

Streptococcus pneumoniae (pneumococcus) is a widely known human pathogen and one of the leading agents in a wide range of infectious diseases but most commonly responsible for bacterial pneumonia, sepsis and meningitis. Pneumococcal related deaths account for 11% of all deaths in children <5 worldwide [1].

In Latin America it is estimated that Streptococcus pneumoniae produces between 1,962,600 and 3,006,800 illnesses yearly and causes between 12,000 and 28,000 deaths in children < 5 years of age with the highest incidences of disease in children >2. Of all the diseases associated with pneumococcus, pneumonia causes the highest number of deaths [2].

Efforts to prevent and control diseases caused by *Streptococcus pneumoniae* as well as to reduce the impact of resistance to antibiotics, have focused on the development of an effective vaccine. In 2007 the World Health Organization recommended routine immunization against pneumococcus and so far 54 countries have introduced the vaccine in their national immunization schedules [3, 4] .

In Colombia vaccination started in 2008 only for children on high risk groups of the disease although in the capital city, Bogotá, the local government decided to subsidized the vaccine for all children born as of October 1, 2008. In 2011 the Colombian government decided to include routine vaccination against *Streptococcus pneumoniae* in its national immunization program. This study was aimed to evaluate heptavalent pneumococcal vaccine effectiveness in children under two years old in Colombia.

Nomenclature

ARI	Acute Respiratory Infection
EPS	Empresa Promotora de Salud (Health Promoting Entity)
ICD	International Classification of Diseases
HR	Hazard Ratio

2. Materials and Methods

We conducted a retrospective cohort study in 2,631 children under two years afiliated to an EPS in Colombia. Children were selected according to the following criteria:

2.1. Exposed

- Children less than two years old that received the complete heptavalent pneumococcal conjugate vaccination regimen between January 1st and the December 31st of 2008.
- Those who were affiliated with the EPS (Health Promoting Entity) and remained affiliated for at least six months after the last dose of the vaccine.
- Residents of Bogotá (Capital city) and surrounding areas.

2.2. Unexposed:

- Those that met the criteria for age and affiliation with the EPS, but only received one dose or did not receive any of the heptavalent pneumococcal conjugate vaccination regimens.

2.3. Criteria for exclusion:

- Children that were vaccinated under the coverage of EPS Compensar, but whose plan of medical care did not include health coverage and as a result did not have any hospitalization records.

Exposure and outcome data was obtained from administrative data bases from the EPS that contain information about vaccination and outpatient and inpatient events codified according to the International Classification of Diseases (ICD-10).

Children were followed for at least six months after the last dose of heptavalent pneumococcal vaccine. The follow up period began when fully vaccinated children received their last dose of pneumococcal vaccine. For unvaccinated children, follow-up started at the mean age when vaccinated children completed their three dose schedule. Only the first hospitalization that occurred at the beginning of the follow-up (which took place around seven months of age) was taken into account. 2,631 children were included in the study, 877 vaccinated and 1,754 not vaccinated.

2.4. Outcomes of interest were:

- Hospitalization due to acute respiratory infections such as bronchitis, bronchiolitis and pneumonia (ICD- 10 codes J128, J129, J158- J160, J180, J189, J205, J206, J209, J210, J218, J219, J22),
- Hospitalization due to other causes potentially related to pneumococcal infection such as meningitis and sepsis (ICD-10 codes G00- G03, A40, A41).
- Hospitalization by otitis media (H650- H652, H659- H662, H669).

2.5. Covariates

In addition to immunization and outcome records, sex, level of economic income and a previous event of hospitalization before vaccination were taken into account. Income was divided in three categories according to the monthly income reported by the parent or guardian of the child. Less than two minimum monthly salaries, between 2 to 5 minimum monthly salaries and above 5 minimum monthly salaries (the minimum wage in Colombia for 2010 was in the order of US$252).

2.6. Analysis

The association between vaccination and pneumococcal disease was evaluated using Cox proportional hazards models [5]. Survival curves were first compared using Kaplan Meier analysis to identify variables with significant differences in survival functions. Then we conducted two types of analysis, one that included all the events of interest (ARIs, meningitis and sepsis), and another in which only pneumonia was considered.

3. Results

2,631 children were included in the study, 88% under the age of 12 months. In the unvaccinated group parent tend to have a lower income than those whose children have been vaccinated (Table 1). 216 children had an event of hospitalization before follow up; most of them were due to acute respiratory infections and neonatal diseases.

301 hospitalizations were registered in total. For children who were hospitalized multiple times, only the first event was analyzed. There were 114 first-time hospitalizations in the unvaccinated group and 42 first-time hospitalizations in the vaccinated group. The total incidence rate of hospitalizations was 11,8 per 1000 children/month. The incidence rate of hospitalization for pneumonia was 3,7 per 1000 children/month.

Kaplan Meier analysis only showed significant differences in survival functions for vaccination status (p= 0,004) and sex (p= 0,001). A previous event was close to significance (p= 0,055) and was therefore included in the multivariate analysis.

Table 1. Characteristics of the children according to their pneumococcal-vaccination status before follow up.

Variable	Vaccinated (N = 877)		Unvaccinated (N = 1754)	
Age group				
< 12 months	775	88%	1550	88%
12 - 24 months	102	12%	204	12%
Male Sex	450	51%	900	51%
Level of income*				
1	438	50%	1334	76%
2	297	34%	355	20%
3	142	16%	65	4%
Hospital admission before follow up	130	15%	216	12%
Hospital admissions during follow up	42	4,8%	114	6,5%

*1. < 2 minimum monthly salaries, 2. 2 to 5 minimum monthly salaries 3. > 5 minimum monthly salaries

(The minimum wage in Colombia for 2010 was in the order of US$252).

Vaccinated children had a significant reduction in the risk of hospitalization for all outcomes (HR 0,58 CI 95% 0,41 - 0,82); when only pneumonia, sepsis and meningitis were included risk reduction was slightly higher (HR 0 ,51 CI 95% 0,31 - 0,85). Male sex was also identified as a risk factor for hospitalization (HR 1,55 CI 95% 1,15- 2,45) (Table 2).

Previous admissions before vaccination were not significant when all ARI hospitalizations were included but became a significant risk factor when including only pneumonia (HR 1,7 CI 95% 1,06-2,93). An additional analysis was done excluding children with one dose of the vaccine from the nonexposed group which yielded similar results. In graph 1, survival functions are presented for both analyses.

Table 2. Characteristics of the children according to their pneumococcal-vaccination status before follow up.

	All events			Pneumonia		
	Exp(β)	CI 95%		Exp(β)	CI 95%	
Sex	1,549	1,151	2,085	1,568	1,029	2,389
Vaccination	0,584	0,414	0,825	0,514	0,310	0,852
Previous hospitalizations	1,439	0,983	2,108	1,767	1,066	2,930

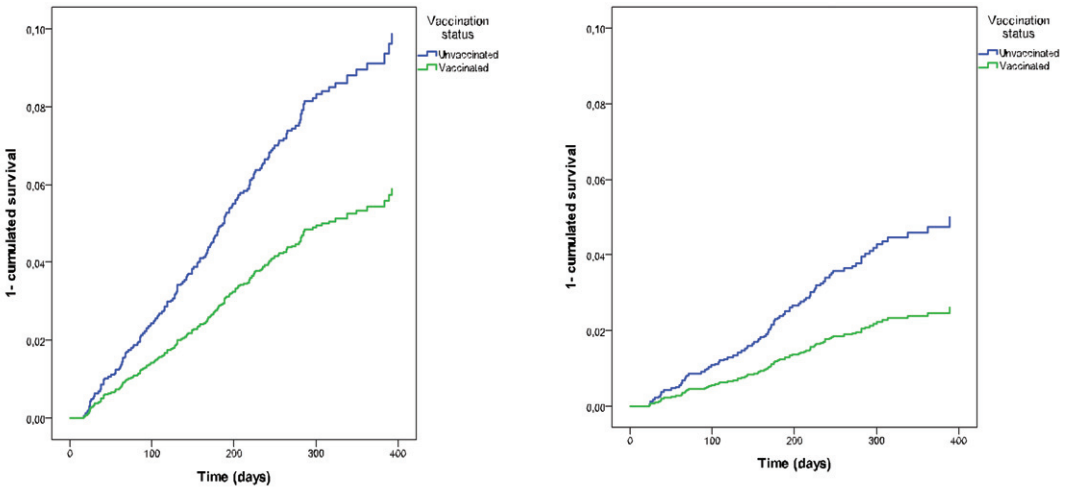

Fig. 1. (a) Function of survival for all events potentially related with infection by *Streptococcus pneumoniae*. (b) Function of survival for pneumonia admission.

4. Discussion

Our results show a significant risk reduction in clinical syndromes potentially associated with pneumococcal infection in children vaccinated with heptavalent pneumococcal vaccine. These results support previous studies of effectiveness available to date [6] that have reported effectiveness between .

Results from an effectiveness study in Uruguay have been recently published showing a 56% reduction in pneumonia admissions, 48% in pneumococcal pneumonia and 59% in pneumococcal meningitis after the introduction of the heptavalent vaccine in the national routine vaccination program [7].

Children in our study were affiliated to the contributive regime, which means their families have a higher income allowing them to pay for their health care insurance; it is possible that vaccine impact would be even greater in children from the subsidized regime who in general live in poorer conditions.

The great variability in the estimations of our results partly represents the difficult in diagnosing pneumonia and other acute respiratory infections, most events correspond to syndromic diagnosis of diseases that have overlapping symptoms. There was no information on how the diagnoses of pneumonia or other similar illnesses were reached. Thus the primary weakness of our study is the availability and quality of the information regarding hospitalization events. However, our results suggest that the vaccination should be able to prevent between 15% and 69% of the hospitalizations due to pneumonia. This would have a large public health impact in Colombia considering that pneumonia is one of the primary causes of infant mortality.

Theoretically a vaccine that would protect against more serotypes could have an even larger impact in reducing the burden of disease by Streptococcus pneumoniae. Colombia has recently decided to replace the heptavalent vaccine with a decavalent one and is in the process of including in the national immunization program for routine administration. This will further reduce the burden of Pneumococcal diseases in the country.

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